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Introductory Remarks

As mentioned in the Administrative Report No. 1 (October 15, 1962), some changes in the personnel have taken place during the contract period. These changes have necessitated some changes in the research programme:

(a) Dr. Y. Løyning left Oslo in June 1962 because he obtained a Research Fellowship at the Australian National University in Canberra (Professor E.C. Eccles). As a consequence, the Research Project No. 1 in the contract was replaced by a study of the "Cerebral control of the motility of the urinary bladder" by Dr. R. Gjone and Dr. J. Setekleiv (cf. below). This study represents a part of our studies on the functional significance of limbic and related structures.

(b) Dr. J. Jansen, who had planned to continue his studies on the afferent projections to the cerebellar cortex (Research Project No. 2 in the Contract), found it necessary to combine this study with experiments on muscle proprioceptors, as explained below. During the spring of 1962 Dr. Jansen was busy building up a new laboratory unit for continuing this work on muscle spindles which he had started while staying in Oxford as a Rockefeller Fellow in 1960-61. Support for equipment was given by the University of Oslo and the Norwegian Research Council. The laboratory unit was completed in the summer of 1962.

The Research Projects Nos. 3 and 4 have been carried out according to the original plans.

(1) Cerebral control of the motility of the urinary bladder (Dr. R. Gjone and Dr. J. Setekleiv).

The role of limbic and cerebral cortical areas in the regulation of the bladder motility and the micturition reflex has been studied. Our knowledge is in particular insufficient concerning the inhibitory control exerted by these areas. Such a study necessitates a background activity which is best achieved by the method of 'direct cystometry'.

This method allows a continuous recording of the intravesical pressure during controlled volume variations. At the same time it reflects the bladder tension in natural micturition.

The entire cerebral cortex has been mapped for excitatory and inhibitory effects. Excitatory bladder responses were obtained from the sensory-motor cortex I and II, and from the supracallosal part of the cingulate region. Inhibitory effects were produced from the somatic sensory-motor cortex I and II and from the subcallosal part of the anterior cingulate region and the orbital gyrus. The study has been completed and represents the most comprehensive investigation in this field ever published. Twenty-five copies of the final paper is ./. enclosed (Excitatory and inhibitory bladder responses to stimulation of the cerebral cortex in the cat. Acta physiol. scand., to be submitted for publication). A preliminary report will be given at the XI. Scandinavian Physiological Congress in Copenhagen, August 1963.

(2) Afferent projections to the cerebellar cortex (Dr. J. Jansen Jr.). See above for changes in the experimental plans.

A large body of evidence indicates that the cerebellum is largely concerned with the control of movement. In order to proceed with the analysis of cerebellar functions it was considered necessary to acquire a better understanding of the more basic spinal mechanisms on which the cerebellum undoubtedly plays. This point of view has been particularly emphasized by the demonstration of two different kinds of efferent nerve fibres to the intrafusal muscle fibres of the spindles and the independent control of the dynamic and static sensitivity of the primary receptors of the spindles (see Jansen & Matthews, 1962).

These considerations form the basis of the experiments which are carried out in the laboratory. The experiments are performed on decerebrate cats. The behaviour of single primary receptors in flexor and extensor muscles to defined mechanical stimuli are compared under

various conditions of reflex drive. The observations allow an estimate to be made of the interplay between nuclear bag and nuclear chain fusimotor activity in various spinal reflex patterns. So far, it appears that flexor spindles in decerebrate cats receive very little maintained fusimotor activity whereas the corresponding systems to extensor spindles are extremely active in the same preparations. This applies to fusimotor activity to nuclear bag as well as nuclear chain fibres. Furthermore, it appears that the flexor fusimotor systems are surprisingly inaccessible to activation by spinal reflex mechanisms. Thus, for instance a crossed extensor reflex is accompanied by a considerable activation of the extensor fusimotor apparatus. In flexor spindles, on the other hand, only very modest changes are observed during flexor reflexes. Several hypothesis can be put forward to explain this difference between extensor and flexor fusimotor activation, and these are at present being tested by experiments. The observations provide additional information about the spinal control of movement and will in addition be a useful basis for investigations on the cerebellar influences in this field.

A preliminary report of the results so far obtained will be presented at the XI. Scandinavian Congress of Physiology in Copenhagen in August 1963.

(3) Search for brain structures of significance for maze learning, passive and active avoidance learning (Drs. O. Kveim, B.R. Kaada and J. Setekleiv).

The experiments have been carried out according to the original plans. The main purpose was to demonstrate more clearly that the three types of learning mentioned in the heading depend upon the integrity of different brain structures, as suggested by previous findings in our laboratory. Maze learning and retention is interfered with by hippocampal lesions; passive avoidance is defective after

removal of areas known to exert a more or less generalized inhibitory influence on somatomotor and various autonomic responses (subcallosal cortex, preoptic area, anterior hypothalamus, orbito-insulo-temporal cortex); active avoidance is reduced by ablation of brain areas facilitating somatomotor and autonomic responses (supracallosal cingulate cortex, part of amygdala).

Electrolytic lesions have been performed in the interpeduncular region and in the brain stem reticular formation, two other regions known to exert strong facilitatory effects on somatomotor activities. In the first group of rats the lesions were made relatively large. Unfortunately this resulted in a relatively high mortality, and in the subsequent groups of animals the lesions were made smaller. The operated rats have been trained in a modified Hebb-William maze, in a passive avoidance situation, and for active avoidance using a modified shuttle box constructed and standardized in our laboratory. It takes several months to perform these tests for each group of animals.

All groups of operated and normal control animals have been tested and most histological sections from the operated rats have been examined. The sections of the last group of animals are at present being prepared. The final analysis of the data therefore must await the results of the complete and detailed histological study.

(4) Cerebral influence on uterine motility (Dr. J. Setekleiv).

As part of our studies on the functional significance of limbic and related structures, the effects of electrical stimulation of these areas on the uterine motility of the oestrogenized rabbit have been investigated.

It was found necessary first to develop a reliable recording technique and to analyse the uterine response to distension, to hypogastric and splanchnic nerve stimulation, and to reflex excitation

and inhibition. The results of these studies will be published in the following five papers which will all appear in the Acta physiologica scandinavica. A final publication will deal with the influence of various brain areas on the uterine motility. These papers will form the main topic of Dr. Setkleiv's postdoctorial thesis:

Uterine motility of the oestrogenized rabbit.

- I. Isotonic and isometric recording of the contractions *in vivo*.
- II. Response to distension.
- III. Further analysis of the response to distension.
- IV. Response to hypogastric and splanchnic nerve stimulation.
- V. Reflex excitation and inhibition.

Ad. I. Isotonic and isometric recording of the contractions *in vivo*. - A technique for isotonic and isometric recording of the uterine contractions *in vivo* has been developed. These two types of recording techniques could be employed simultaneously and separately in the two horns of the uterus (twin uterus preparation). The myometrium was stimulated by increasing doses of noradrenaline and oxytocin, or by electrical stimulation of the hypogastric nerve at increasing strengths. The isotonic response soon reached a maximum, whereas the isometric response revealed a gradual increase. Thus, the isotonic response can be maximal at submaximal stimulation and is a less reliable quantitative measure of the strength of contraction.

Ad. II. Response to distension. - The oestrogenized rabbit uterus was distended either by increase in the intrauterine pressure (isotonic recording) or by increase in the intrauterine volume (isometric recording). The behaviour of the uterus in response to distension has been described as the response of a stretch receptor - myo-effector system.

The effect of the stimulus (distention) on the stretch receptor is modified by a time-dependent viscous element.

The discharge of the stretch receptor plays on two different myometrial responses: (i) an initial contraction - the stretch response, and (ii) rhythmic contractions. The former responds to changes in distention (the dynamic response), the latter to sustained distention (the static response). The characteristics of the stretch response to various degrees of rapid distention, and to repetitive distention, have been described. Also, the effect of increase in intrauterine pressure and volume on the rhythmic activity has been analysed.

Repetitive distention produced potentiation of the myometrial response and from the rhythmic variations of the stretch response the latter response was found to be an indicator of the myometrial excitability.

Adaptation of the stretch receptor is brought about by reduction of the intrauterine pressure which diminish the pacemaker activity.

Ad. III. Further analysis of the response to distension. - The mechanisms underlying the myometrial response to distention, the stretch response, and the change in rhythmic activity has been further analysed.

Changes in rhythmic activity were obtained independently in the two uterine horns (with or without spinal anesthesia). These results indicate that the rhythmic activity is independent on hormonal agents and spinal reflexes. - In order to determine whether the stretch response is initiated by local reflexes with release of a transmitter substance or by a myogenic mechanism, the influence of autonomic blocking agents and local anesthesia were studied. The experiments indicate a myogenic origin of the response.

Based on the results of the influence of various drugs, the following aspects of myometrial activity are discussed: (i) the possibility of different mechanisms in the initiation of the rhythmic

activity and the stretch response, (ii) the mechanisms of the increased minimum pressure, and (iii) the different influence on the contractile property of the myometrium by the nervous transmitters.

Ad. IV. Response to hypogastric and splanchnic nerve stimulation. - Electrical stimulation of the hypogastric nerve elicits a contraction of the uterus which is followed by a period when the rhythmic activity is diminished or completely abolished.

The response to hypogastric nerve stimulation varies with the frequency of stimulation. After short-lasting stimulation, maximal contractions were obtained at frequencies between 30 and 50 cps. With long-lasting stimulation, low frequencies (5-10 cps) elicited a series of contractions. Frequencies above 10 cps in addition elevated the minimum pressure. The mechanism underlying the increase in minimum pressure has been discussed. The elevated minimum pressure was not maintained during continuous stimulation. Following factors have been discussed as the cause of this decrease: (i) change in transmitter output, (ii) influence of the transmitter on the membrane activity or the cell metabolism, and (iii) mechanical change due to the contractile or passive properties of the myometrium.

The most "economic" frequency, or the best utilization per stimulus, in the production of contractions was found to be about 10 cps, as indicated by a maximal contraction to a constant number of impulses. This response has been discussed in the light of what is known about facilitation of junction potentials.

Evidence for cholinergic fibres in the hypogastric nerve was not obtained. The depressive effect of atropine may be due to influence on the myometrium and the effect of neostigmine to "overflow" of acetylcholine. The failure of cocaine to potentiate the uterine response when administered i.v. is explained by the liberation of adrenaline. Potentiation was obtained by intra-uterine application of cocaine.

The response to splanchnic nerve stimulation differed from the response to hypogastric nerve stimulation by a longer latency and by a more gradual onset consisting of several increasing contractions.

Ad V. Reflex excitation and inhibition. - The myometrium has been found to respond with contractions to mechanical stimulation of the rectum and to various stimuli which activate the sympathetic-adrenal system (stimulation of the central cut end of peripheral nerves, occlusion of both carotides and asphyxia). Such activation occurs also during the low blood pressure caused by stimulation of the peripheral end of the vagus nerve.

Reflex inhibition of the myometrium has not previously been reported. In the present investigation inhibition of the rhythmic activity was obtained after depressor nerve stimulation. The pathways for the responses has been determined.

Reprints of all papers resulting from this research programme will be forwarded to the EO.OAR as soon as they appear in the journals.

Excitatory and Inhibitory Bladder Responses to
Footnote 1 Stimulation of the Cerebral Cortex in the Cat 1)

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Running title: Bladder responses to brain stimulation

Abstract

A continuous intravesical pressure recording was established in 22 cats anesthetized by operative canalization of the bladder cavity, leaving the urinary outlet intact. The intravesical pressure variations caused by controlled volume changes were studied, and the alterations in bladder activity in response to stimulation of the cerebral cortex were recorded. The following excitatory bladder reactions on cortical stimulation are described: augmentation of the rhythmic contractions, dropwise expulsion of the bladder contents with incomplete emptying of the vesical cavity and, finally, a normal micturition act with forceful detrusor contractions. With regard to inhibitory effects the following responses were obtained: reduction or complete inhibition of the rhythmic bladder activity, arrest of the urination act or suppressed micturition.

In agreement with previous investigations excitatory bladder responses were obtained from the first sensory-motor area and from the anterior cingulate region. In addition, excitatory effects were elicited by stimulation of the anterior ectosylvian and anterior sylvian gyri (the somatic sensory-motor area II).

Previous observations of inhibitory influence on bladder activity from the first sensory-motor area were confirmed. In addition, inhibitory effects were produced from the somatic sensory-motor area II, the subcallosal part of the anterior cingulate region and the orbital gyrus. All the various types of bladder reactions described above were obtained from any of these regions.

Introduction

The influence of the cerebral cortex on the activity of the urinary bladder has been the subject of only a few systematic experimental studies. In particular, very little is known about inhibition (arrest of micturition and relaxation of the bladder) in response to cortical stimulation. The main purpose of this study was to localize the cortical areas influencing bladder motility both with regard to excitation and, in particular, inhibition.

The first evidence of cortical excitatory influence on the bladder function was presented by Bochefontaine (1876) who observed bladder contractions in the curarized dog on faradization of the cortex surrounding the cruciate sulcus. This observation was confirmed, in experiments on cats and dogs, by Bechterew and Mislawsky (1888). These workers recorded intravesical pressure elevation in response to stimulation of the medial part of the posterior sigmoid gyrus in the curarized animal. Similar effects from the sensory-motor cortex were later obtained in the dog by Frankl-Hochwart and Frölich (1904) and in the cat by Hunsicker and Spiegel (1933) and Langworthy and Kolb (1935). Crouch and Thompson (1939) observed micturition resulting from stimulation of the same cortical region in cats, dogs and monkeys.

During the past two decades systematic studies have also revealed excitatory bladder responses from the posterior orbital region in dogs (Okinaka et al. 1955), the anterior cingulate area of the cat (Strøm and Uvnäs 1950, Ingersoll, Jones and Hegre 1961), the posterior cingulate region in dogs (Kremer 1947) and cats (Henneman 1948), the prepyriform cortex of the dog and cat (Koikegami et al. 1957) and the posterior pyriform cortex in cats (Henneman 1948, Smith 1949). From the latter area Kaada (1951) elicited urination (as well as defecation) in cats, dogs and monkeys.

Inhibitory bladder responses, recorded by a fall of the intravesical pressure, have been elicited from the sensory-motor cortex (Hunsicker and Spiegel 1933, Langworthy and Kolb 1935). In addition, relaxation of the

bladder has been observed by stimulation of the posterior cingulate and pyriform cortex (Henneman 1948).

In the experimental studies referred to above, the excitatory and inhibitory bladder responses were recorded as alterations in the intravesical pressure either by the use of a urethral catheter, or by operative canalization of the bladder cavity through a cystostomy. When the latter procedure was employed, the neck of the bladder was ligated to provide a closed cavity, from which no leakage could then occur during the intravesical pressure recording. In both cases the micturition reflex was abolished by the suspension of the sphincter mechanism.

In order to gain further knowledge about cortical regulation of bladder activity it was considered essential to modify the recording technique so as to include the dynamics of the micturition act, thus ^a facilitating/study of the way this act is influenced by cortical stimulation. The experimental conditions required may be achieved by utilizing the technique of 'direct cystometry' (Murphy and Schoenberg 1960). By this method the urinary outlet is left fully intact, the intravesical pressure readings being obtained through a bladder puncture. In the present experiments it was found more convenient to perform a cystostomy, maintaining the advantage of an undisturbed sphincter mechanism.

Material and Methods

A total of 22 cats of both sexes (weight 1.4-4.2 kg) were used.

The entire experimental procedure was carried out under general anesthesia, usually by intraperitoneal administration of 1 per cent chloralose ²⁾

Footnote 2

(40 mg/kg) and 25 per cent urethane (500 mg/kg). Two animals were given paralyzing doses of succinylcholine, Curacit ^(R) Nyco ²⁾, (1 mg/kg) and ventilated artificially with pure oxygen through a tracheostomy. In these cases anesthesia was induced by injections of chloralose alone, using the regular dose. Three animals were given Nembutal ^(R) Abbott

(30 mg/kg).

Cystostomy was performed through a midline abdominal incision and a Nelaton catheter No. 12 was inserted into the fundus region and sutured to the bladder wall. By means of a Statham pressure transducer connected to a Grass polygraph (Model 5 C) with DC-amplifiers a continuous intravesical pressure recording was established. Blood pressure and respiratory movements (represented by the excursions of the thoracic wall) were recorded simultaneously on the same polygraph in 9 and 6 animals, respectively. In the first three experiments the bladder response was obtained by means of the 'closed system method' using an intravesical balloon, whereas all subsequent experimental data were based upon the modification of the 'direct cystometry' mentioned above. By this technique an isometric recording of the intravesical pressure is obtained, as long as no urination takes place. In addition, the pressure changes during the voiding act are recorded. After replacing the urine by saline solution at body temperature, the bladder volume could be checked through the 3-way tube connecting the catheter to the transducer.

The animal's head was fixed in a Horsley Clarke frame and a craniotomy performed, the cerebral cortex being exposed to the extent required. The cerebral cortex was stimulated by electric square waves of 1 msec' duration and applied at different frequencies (1-100 cps) through bipolar, silver-chlorided, ball-tipped electrodes with an interelectrode distance of about 2 mm. The stimulus strength necessary to elicit bladder responses was 2-4 volts. In mapping the cortical surface intensities of 5-7 volts were ordinarily used. Stimulation of the cerebral cortex was not started until 3 hours after the induction of anesthesia.

Results

(A). Background activity

Rhythmic variations of the intravesical pressure were constantly

recorded in the anesthetized animal. These pressure changes, representing detrusor contractions in response to distention of the bladder, were seen not only during the standard chloralose-urethane anesthesia, but also

Fig. 1 when nembutal was used (Fig. 1). The frequency and amplitude of the detrusor contractions were increased by increasing distention of the bladder until finally micturition occurred. The micturition threshold, *i.e.*, the degree of bladder filling necessary to precipitate urination, showed individual variations from 10 to 75 ml, and was regularly found to be higher in the anesthetized male cats than in the females. The bladder capacity seemed to bear no definite relationship to the body weight, but was clearly dependent on the type of anesthesia. Thus the micturition threshold was significantly higher under nembutal as compared with chloralose-urethane anesthesia. To demonstrate this phenomenon further, 20 mg nembutal/kg body weight was added, in one experiment, to the standard dose of chloralose-urethane, 3 hours after the administration of the latter. The bladder capacity was raised thereby from 10 to 65 ml.

Under ordinary conditions this critical intravesical volume did not, however, vary significantly in one and the same animal throughout the experiment, not even during successive cystometrics performed by step-wise bladder filling at intervals of 3 to 5 minutes. As shown in Fig. 2 each volume increment caused a sharp pressure rise, followed by a slow return to a stable tension level. The latter represented a very slight elevation of the intravesical pressure as compared with the preceding level.

(B). Bladder responses resulting from electrical stimulation of the cerebral cortex.

In the summary diagrams of the responsive cortical areas (Fig. 8) the stimulation effects are referred to simply as excitatory (↑) or inhibitory (↓). It should be emphasized, however, that the two symbols represent different types of bladder reaction. Thus an excitatory response includes augmentation of the rhythmic detrusor contractions

Fig. 3

(Fig. 3A) as well as precipitation of a voiding act. The latter was observed either as an abortive type of micturition with drop-wise, incomplete expulsion of the bladder contents (Fig. 3B) or as sustained detrusor contractions with complete emptying of the vesical cavity (Fig. 3C and Fig. 4). All of these excitatory responses occurred after a latency of 2-3 seconds, and the optimal effect was reached at a stimulus frequency of 50 cps.

Fig. 4

Inhibitory stimulation effects were recorded as a diminution or

Fig. 5

abolition of the rhythmic bladder activity (Fig. 5), arrest of micturition (Fig. 6 and Fig. 7B), or prevention of the onset of urination (Fig. 7C - D).

Fig. 6

Arrest of micturition could be demonstrated irrespective of the urination reflex was initiated by cortical stimulation or resulted from bladder distention. A latency of 2-3 seconds was found also in all types of inhibitory bladder response, this being recorded as a prompt and marked reduction of the intravesical pressure. A drop of tension to below the resting level (as recorded in the intervals between two successive, spontaneous detrusor contractions) was often encountered. On cessation of stimulation a sharp pressure rise was frequently observed with restoration of the pre-stimulation tension level. In some cases, however, a post-stimulation inhibition of long duration (2-3 min) was obtained.

Fig. 7

Suppression of the urination mechanism could be produced when cortical stimulation was started prior to a rapid bladder filling beyond the volume which would ordinarily release the micturition reflex in that particular experiment. In Fig. 7C the stimulus was applied to an inhibitory point of the cerebral cortex 15 seconds before the filling of the bladder. A delay of urination is shown, lasting until cessation of the cortical stimulation. As illustrated in Fig. 7D, the voiding act could also be completely inhibited. Inhibitory bladder responses were obtained by the same stimulation parameters which gave optimal excitatory effects. They were, however, elicited within a wider frequency limit, from 5 to 50 cps,

being maximal between 20 and 50 cps.

During exploration of the responsive cortical regions the same type of bladder reaction could be readily and repeatedly reproduced from each point of stimulation. In the same animal opposite stimulation effects were, however, regularly observed on shifting the site of the electrodes.

The rhythmic bladder activity, as well as any effect of cortical stimulation, were depressed by deepening the anesthesia.

The cortical origin of the excitatory and inhibitory bladder responses was demonstrated by the fact that local application of 1 per cent lidocaine (Xylocain (R) Astra) to the cerebral cortex abolished the effects, whereas the rhythmic activity of the bladder was not interfered with.

The genuineness of the bladder responses. One might question whether the hydrostatic pressure changes recorded from the vesical cavity did, in fact, reflect exclusively variations in bladder activity. Several factors which might be assumed to influence the dynamics of the bladder, have to be considered:

Firstly, the possibility that the intravesical pressure changes are secondary to alterations in respiratory movements is excluded by the demonstration of their presence in the curarized and artificially ventilated animal. As shown in Figs 4 and 6 the rhythmic detrusor contractions were not altered by giving paralyzing doses of succinylcholine; marked stimulation effects, excitatory (Fig. 4) as well as inhibitory (Fig. 6), were readily elicited.

Secondly, contractions of the abdominal muscles may affect the intra-abdominal pressure and thereby might be assumed to influence the bladder activity. However, the presence of bladder responses in fully curarized animals also proves them to be independent of this factor. Further, definite bladder responses were frequently observed without any visible movements of the abdominal wall.

The probability remains that alterations in gastrointestinal

movements may act directly upon the bladder wall and in this way may interfere with the stimulation effects. This is strongly contradicted by the fact that forceful, ileus-like bowel contractions (visible by external abdominal inspection), resulting from stimulation of the vagus nerve, did not affect the intravesical pressure, as recorded on the polygraph.

Localization of the responsive cortical regions. The topographical distribution of the cortical points which have been stimulated in the present experiments appear on Fig. 8. No change in the bladder activity resulted from stimulation of extensive areas on the lateral and medial aspects of the hemispheres and the olfactory bulb. Most of the temporal lobe, including the hippocampus, was not explored. This will be done in a subsequent study which also deals with the effects of stimulation of the amygdaloid and periamygdaloid region. Significant stimulation effects on the bladder activity were obtained from the following cortical regions:

1. The first somatic sensory-motor cortex. - This region was explored in 12 animals in which a total of 60 stimulations were applied. 28 excitatory and 19 inhibitory responses were obtained, whereas 13 stimulations produced no bladder response. Both types of bladder reaction were encountered in all the 12 cats, although at times excitatory or inhibitory stimulation effects predominated. On the lateral aspect of the hemisphere, the responsive loci occupy the upper portion of the pericruciate cortex, and the anterior as well as the posterior sigmoid gyri. The effective zone seems to include the region of the lower extremities and trunk, whereas the region of the upper extremities and the head is unresponsive. On the medial aspect of the hemisphere, excitatory effects were mainly obtained from the anterior sigmoid gyrus, whereas inhibitory reactions predominated when stimulating the posterior sigmoid gyrus.

2. The anterior ectosylvian and anterior sylvian gyri, corresponding to the somatic sensory-motor area II as outlined by Woolsey et al. (1958, 1959). - This region, like the pericruciate cortex, yielded both types of bladder response. However, in 2 of the 5 animals, in which this cortical region was explored, inhibitory effects only were recorded. Excitatory as well as inhibitory responses were produced in the remaining 3 cats. As a whole the stimulation effects were not as readily obtained from this area as from the first somatic sensory-motor cortex. They seemed to depend more on the animal being in good condition and a relatively light anesthesia.

3. The anterior cingulate cortex (Fig. 8B). - The different character of the bladder response allows a clear subdivision of this area into two zones, one lying superiorly and bordering the genu of the corpus callosum, the other lying inferiorly in the subcallosal part of the cingulate gyrus. Stimulation of the supracallosal and pregeniculate cortex was performed in 8 animals, consistently resulting in bladder excitation. In 4 of the same cats the subcallosal part of the anterior cingulate region was exposed. All of them responded to stimulation of subcallosal points, giving inhibitory bladder effects exclusively.

4. The orbital gyrus (Fig. 8A). - The bladder reactions produced by stimulation of this region were consistently of the inhibitory type. Such effects were obtained in 7 animals, in which a total of 28 stimuli were applied. Four of these stimulations caused no change in the bladder activity, whereas inhibition occurred 24 times.

(C). Concomitant changes in blood pressure and respiratory movements.

In accordance with previous observations (for references, see Kaada 1951, 1960, Uvnäs 1960 and Lofving 1961) alterations in blood pressure and respiratory movements were recorded by stimulation of all the cortical regions found to yield bladder responses.

Effects on blood pressure. - The pressure alterations, as recorded

from the femoral artery, were in general slight and inconstant. This fact may probably be related to the type and depth of anesthesia used in the present study. No definite correlation was shown to exist between the direction of the pressure alteration in the femoral artery and in the vesical cavity. The diagrams in Figs. 5 and 6 serve to illustrate this independence by showing two cases of bladder inhibition, one being accompanied by a blood pressure fall and the other by a slight elevation.

Effects on respiratory movements.— In general the respiratory responses were the same as those reported previously. As a rule these stimulation effects were more marked and more readily obtained than the blood pressure changes. The most striking influence on the respiratory movements was elicited from the orbital and anterior cingulate regions, from which an initial complete arrest in expiration was produced (Fig. 3A), usually followed by a period of lowered respiratory frequency. The somatic sensory-motor areas I and II yielded weaker respiratory responses, but acceleration as well as slowing of the respiratory rate were frequently observed.

Discussion

The present experiments demonstrate that during chloralose-urethane or nembutal anesthesia rhythmic bladder contractions can be recorded in the cat. The frequency and amplitude of the contractions are augmented by increasing bladder distention, which finally results in urination.

Previous cortical stimulation experiments have chiefly been concerned with the influence on the rhythmic bladder activity. The recording technique used in the present investigation allows in addition a comparison of the influence on the rhythmic detrusor contractions and the micturition reflex. All the responsive areas were shown to produce either of these effects, both as regards excitation and inhibition. However, the latter was often significant only when demonstrated by the

interruption of micturition.

The following excitatory stimulation effects have been demonstrated: (i) augmentation of the rhythmic detrusor activity, (ii) the initiation of repetitive and strong contractions resulting in dribbling urination, and finally (iii) a sustained detrusor activity representing the normal micturition act with full emptying of the bladder. The present investigation confirms the earlier experimental evidence of an excitatory influence on the bladder activity from the first somatic sensory-motor cortex and the supracallosal part of the anterior cingulate region. In addition, excitatory (as well as inhibitory) bladder responses have been elicited from the anterior ectosylvian and anterior sylvian gyri, corresponding to the somatic sensory-motor area II, as delineated by Woolsey et al. (1958, 1959). This is, to the authors knowledge, the first demonstration of an autonomic response to stimulation of this area.

Excitatory stimulation effects were not obtained from the posterior cingulate gyrus, as previously observed in the dog (Kremer 1947) and cat (Henneman 1948). However, in the present study this region was stimulated under relatively deep anesthesia, which may possibly account for the failure to produce such effects.

In accordance with previous observations (Langworthy and Kolb 1935, Spiegel and Hunsicker 1936) inhibitory bladder reactions were demonstrated by cortical stimulation of the first somatic sensory-motor cortex. Further, bladder inhibition was, in the present study, elicited also from the somatic sensory-motor area II, from the subcallosal part of the anterior cingulate gyrus, and from the orbital region. The two latter regions yielded inhibitory responses exclusively, and the effects were strong and readily obtained, especially as far as the influence on the micturition act was concerned. Thus, within the anterior cingulate area there appear to be two distinct zones, one exerting an excitatory and one an inhibitory influence on the bladder activity. A similar differentiation has been made by Kaada (1951, 1960) with regard to the effects on somatomotor

activities and partly on respiration and blood pressure. Further, it is of considerable interest that, in the cat, bilateral ablation of the same two zones results in different behavioral manifestations (McCleary 1960, Kaada, Kveim and Rasmussen 1962). In contradiction to the results of the present investigation Koikegami et al. (1957) reported no inhibitory effects on the bladder activity by stimulation of the orbital gyrus. This discrepancy may be due to differences in the experimental techniques. The latter investigators recorded the intravesical pressure either by the use of an intravesical balloon or by establishing a closed cavity by means of a catheter. Thus the effect on the micturition act, which appears to be of special importance in studies of the inhibitory influence, could not be observed. Bladder inhibition was also produced by stimulation of the pyriform cortex through needle electrodes. Such stimulation was carried out in two animals in addition to the usual experimental procedure (Fig. 5).

The short latency of the bladder responses proves that they are mediated by nervous activity and not through a humoral mechanism. The cortical origin of the effects is demonstrated by their disappearance on surface anesthesia of the responsive cortical locus. A study of the pathways mediating the impulses from the responsive cortical regions will be dealt with in a subsequent communication.

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FIGURE LEGENDS

Fig. 1. Rhythmic 'spontaneous' activity of cat bladder. Above: chloralose-urethane anesthesia. Below: nembutal anesthesia.

Fig. 2. Cystometrogram obtained by step-wise filling of the bladder during chloralose-urethane anesthesia.

Fig. 3. Excitatory stimulation effects on bladder activity and concomitant changes in blood pressure and respiratory movements. Stimuli of 1 msec.'s duration were applied at 5 volts to the cortical areas indicated by arrows. A. Intravesical pressure rise in response to stimulation at a frequency of 50 cps. B. Drop-wise urination elicited at 5 cps. C. Micturition in response to stimulation at 50 cps.

Fig. 4. Curarized animal. Micturition, accompanied by a marked rise in intravesical pressure resulting in complete emptying of the bladder. Point indicated by arrow stimulated with 4 volts at 50 cps.

Fig. 5. Inhibition of the rhythmic bladder activity and concomitant fall of blood pressure elicited from the pyriform cortex, using 5 volts and 50 cps.

Fig. 6. Curarized cat. Interruption of urination, initiated by rapid bladder filling, by stimulation (5 volts, 50 cps) of the point indicated by arrow in anterior cingulate region. The inhibitory effect was succeeded by an immediate intravesical pressure rise and re-occurrence of micturition on cessation of stimulation.

Fig. 7. Interruption (B) and inhibition (C,D) of normal micturition act (A) initiated by rapid bladder filling. These inhibitory responses were obtained from the area indicated by arrow on the inset. The duration of the inhibition corresponds to the stimulation period. Stimulus parameters: 1 msec., 7 volts, 50 cps. The effects shown in C and D were produced when stimulation was started 15 sec prior to the bladder filling.

Fig. 8. Bladder responses to stimulation of the cerebral cortex in cats.
A. Lateral aspect of the cerebral hemisphere; B medial aspect.
Excitation, ↑, inhibition, ↓, and no response, 0.